LETTER TO THE EDITOR

Goserelin Cannot Improve the Weakness of a Patient with Kennedy Disease after 40-Week AdministrationZhi-Guang Shi,^{1,4} De-Ke Jiang,² Mei Zhao³ & She-Qing Zhang¹¹ Department of Neurology, Shanghai Changhai Hospital, Shanghai, China² Institute of Genetics, Fudan University, Shanghai, China³ Department of Interventional Neurology, Shanghai Oriental Hospital, Shanghai, China**Correspondence**

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Kennedy disease (KD), also known as X-linked spinal and bulbar muscular atrophy, was first described by Kennedy in 1968. It is characterized by slowly progressive bulbar and proximal muscle weakness. Other symptoms include gynecomastia, tremor, testicular atrophy, impotence, and infertility. Distal muscle involvement may be later detectable in an advanced course of disease [1]. The molecular basis of KD is the expansion of a trinucleotide CAG repeat in the first exon of androgen receptor (AR) gene. The CAG repeat within normal individuals ranges from 11 to 35, but varies between 40 and 62 repeat in KD patients [2]. What is particular in the pathogenesis of KD is the ligand-dependent mechanism, because the mutant AR has a specific ligand, testosterone [3]. In the last decade, many studies have demonstrated that chemical or surgical castration may improve the symptoms in KD transgenic models [4,5]. This raised the possibility to treat KD patients using presently approved drug. Recently, a clinical trial of leuporelin on 50 KD patients for 48 weeks has shown some beneficial effects in a phase 2 study [6]; but another multicentre, randomized, double-blind placebo-controlled clinical trial of leuporelin treatment on 204 KD patients for 48 weeks did not show a significant effect on swallowing function [7]. Goserelin has been extensively used in the treatment of prostate cancer, but it has not been tested in KD patients before. Therefore, we administered goserelin on a patient clinically and genetically diagnosed with KD for 40 weeks. In surprise, the drug did not produce any beneficial effects on muscle strength, but bring about impotence and breast enlargement.

The patient is a 42-year-old man. At the age of about 20, he found that he could not stretch his fingers easily after clenching the fists. If he turned his head to the right exertionally, he had to

wait a moment to turn it to the left and vice versa. This tonic spasm of muscle after forceful voluntary contraction occurred, especially in cold weather. Repeated contractions wore it out, but gentle movements did not evoke this phenomenon. This symptom lasted about fifteen years. He did not feel painful muscle cramps in the gastrocnemius or other muscles. Several years later, he felt fasciculations in his face and forearms, and gradually fasciculations occurred on all his body except the tongue. Since the age of 38, he found the difficulties in climbing upstairs especially when he carried heavy things. His weakness gradually worsened, and he began to notice the thighs becoming thinner and thinner. At the age of 39, he began to feel the difficulties in using his distal leg and hand muscles, for example, he could not stand up on his toes or on his heels. Sometimes, his legs were unexpectedly hurt, but he could not feel it. With the worsening of his weakness, the myotonia and fasciculations gradually ameliorated. At the age of 24, he married a healthy woman and had a child later. He did not complain of impotence. On examination, he was 170 cm tall and 60 kg in weight. His intelligence, visual acuity, and swallowing functions were normal. There was no atrophy in his face and tongue. He showed mild to moderate proximal muscle atrophy and weakness, hypotonus, and hyporeflexia in the limbs. His hypotenar muscles showed mild atrophy. After brief percussion, a muscular eminence would be noticed in his biceps brachii. He walked with steppage gait. His sensory system to touch, pinprick, and temperature was mildly to moderately disturbed, but the position and vibration sense was normal. His blood creatine phosphokinase was 1750 u (normal range 25–200), but the electrolytes and glucose in the blood were normal.

Figure 1 Gene sequencing reveals the CAG repeat in the exon 1 of androgen receptor gene is 53 copies, shown between the two arrows.

The patient was clinically diagnosed with KD. To verify the diagnosis, we determined the sequence of the first exon of the AR gene. After informed consent was obtained, we collected the peripheral blood for genomic DNA extraction according to standard procedures. The CAG repeated sequence in the exon 1 of AR gene was amplified, using the following primers: 5'-CCAGAATCTGTTCCAGAGCGTGCG-3' and 5'-GCTGTGAAGGTTGCTGTTCTCAT-3'. PCR-amplified fragments were separated by agarose gel electrophoresis, as previously described [2]. To precisely determine the number of the CAG repeats, the DNA fragments were directly sequenced by DNA analyzer (Foster City, CA, USA). The sequencing result showed that the patient had 53 CAG repeats (Figure 1).

After informed consent was obtained, we administered goserelin by subcutaneous injection into the anterior abdominal wall. The injected dose is 3.6 mg, every 28 days, for 40 weeks. In surprise, after 40 weeks of treatment, the symptoms of weakness did not improve at all; his ability of daily living (ADL) scores worsened from grade 1 to grade 2, according to the methods previously described. Briefly, ADL score was assigned as follows: 0 = normal; 1 = mild weakness of limb muscles, climbs stairs easily but aware of weakness; 2 = mild to moderate weakness, climbs stairs with difficulty and generally uses a cane; and 3 = moderate to severe weakness, uses a wheelchair most of the time or mostly recumbent [8]. In addition, he suffered impotence and enlarged breasts. Therefore, he discontinued the therapy.

Goserelin is an analogue of synthetic luteinizing hormone-releasing hormone (LHRH). Chronic administration can reduce testosterone production, the levels of which remain within the castrate range for the duration of treatment [9]. In view of the ligand-dependent pathogenesis of KD, many researchers believe that suppression of

testosterone can retard or halt the progression and ameliorate the neurological deficits; however, our patient did not show any improvement after 40-week treatment. Although we did not determine the concentrations of testosterone in the blood during the course, the side effects of impotence and enlarged breasts might indicate that the hormone had reduced. We admit that we only intend to report the fact that goserelin did not improve the weakness after 40 weeks of administration. We do not know whether this drug is not effective to the patient or the disease has progressed naturally, because of the coherent limitation of case report.

Although previous transgenic animal studies demonstrated that testosterone plays a crucial role in the progression of symptoms in KD pathogenesis, a recent study by Chevalier-Larsen and Merry [10] showed that testosterone treatment fails to accelerate disease in a transgenic mouse model of KD. These paradoxical conditions might raise question about the potential target of androgen reduction therapy.

Acknowledgments

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Disclosure

This work was approved by the ethnic commission of Second Military Medical University.

Conflict of Interest

The authors declare no conflict of interest.

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